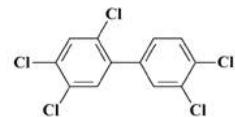




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2,3',4,4',5-Pentachlorobiphenyl (PCB 118)



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National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors
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Rationale for study of PCB118

- Highest human exposure for mono-ortho class of PCBs
 - 95th percentile- 46.6 ng/g lipid in serum (NHANES 2001-2)
- Has partial dioxin-like activity
 - TEF (WHO-1998) = 0.0001 (100×10^{-6})
 - Reevaluation of WHO TEFs (Vandenberg et al 2006)
 - TEF (WHO-2006) = 0.00003 (30×10^{-6})
- Mixed P450 inducer
 - Dioxin-like and Phenobarbital-like activity



Study Design

- Female Harlan Sprague-Dawley rat only
 - Oral gavage: 5 days per week up to 2 years
 - Vehicle: corn oil:acetone (99:1) - 2.5 ml/kg
- Doses
 - 0, 100, 220, 460, 1000, 4600 ug/kg
 - Additional doses: 10ug/kg, 30ug/kg
 - 14, 31 and 53 week interim time points
 - Stop-study: 4600 ug/kg (cease dosing at 30 wks)
- Dose rationale based on
 - Equivalence to TCDD study doses 3-100 ng TCDD/kg (TR 521)
 - Added 4600 ug/kg dose in case potency was lower than predicted by TEF



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PCB118 purity determination

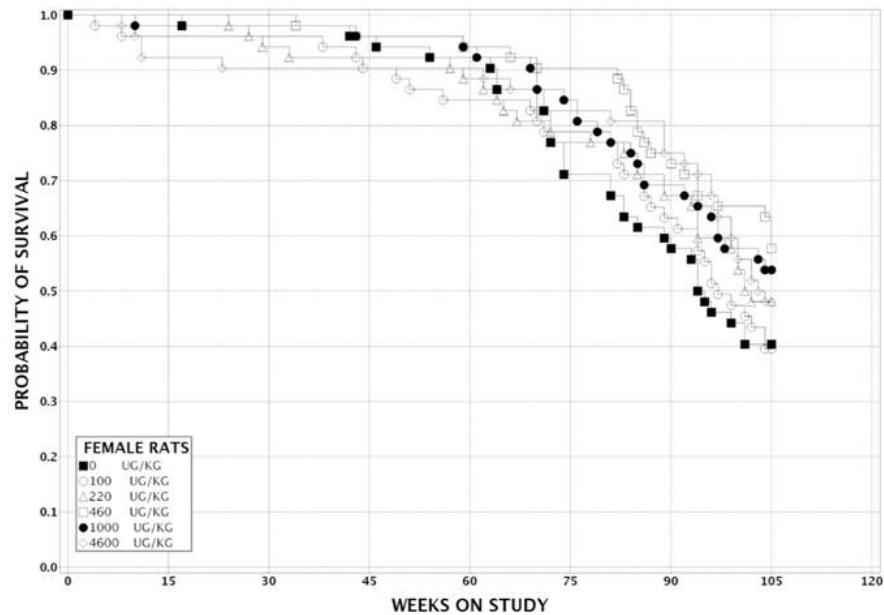
- PCB 118 is a weak DLC; TEF=0.0001
 - Presence of low levels of high potency byproducts was of concern
 - Technical report 531- PCB126:PCB118 binary mixture
 - Initial designed as study of PCB118 alone
 - Identification of PCB126 as a synthetic by product- 0.6% of PCB118 bulk
 - Majority of dioxin-like activity due to PCB126 (TEF=0.1)
- PCB118 synthesized for current study
 - Purity evaluated using TEF based purity criteria
 - Ensure that dioxin-like activity is attributable primarily to PCB118
- TCDD Toxic Equivalents (TEQ) in bulk PCB118
 - 0.39 ng TEQ/1000ug PCB118 (based on WHO-1998 TEFs)
 - Highest contributor: PCB156 (TEF = 0.0005) present at 0.06%
 - 0.123 ng/TEQ/1000ug PCB118 (based on WHO-2006 TEFs)



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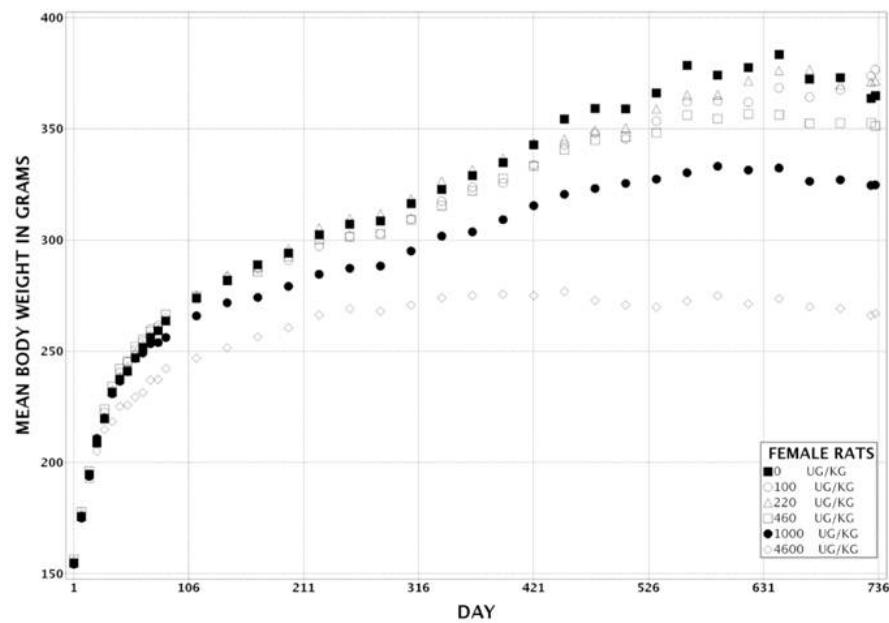
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No effect on survival





Depression in body weight gain in groups >460 ug/kg





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Disposition data for PCB118

- Dose dependent increase in tissue levels
 - Adipose > liver > lung > blood
- 14, 31 and 53 week data comparable
 - Higher at 2 years
- Liver-adipose ratios <0.2
 - Most DLCs: liver: adipose ratio is >3
 - Sequestration in the liver by CYP1A2
 - Suggests no CYP1A2 binding by PCB118



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Mechanism-based endpoints

- Increase in CYP450 1A and 2B
 - Increased in liver at all time points in all dose groups
 - 40-fold increase in CYP1A1
 - 7-fold increase in CYP1A2
 - 23-fold increase in CYP2B
 - 77-fold increase in lung CYP1A1
- Increase in hepatocyte proliferation
 - Increased in the 4600 ug/kg only at all weeks
- Thyroid hormones
 - Decreased serum free and total T4 at all weeks
 - Due to induction of UGT1A1
 - No effect on T3 or TSH



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Tissue weights -Lowest dose where effect observed (ug/kg)

Endpoint	14wk	31wk	53wk
Liver weight	1000	1000	1000
Relative liver weight	460 (+30)	460	1000
Relative Kidney	NS	4600	1000
Lung	NS	NS	NS
Relative lung	NS	4600 (1.15x)	NS
Spleen (decrease)	NS	4600	4600
Relative spleen	NS	4600	NS
Ovary	220 only	NS	NS
Relative ovary	NS	NS	NS
Thyroid	NS	NS	220 only
Relative thyroid	NS	NS	NS
Thymus	NS	NS	NS



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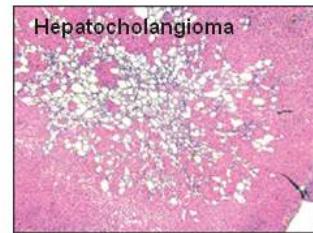
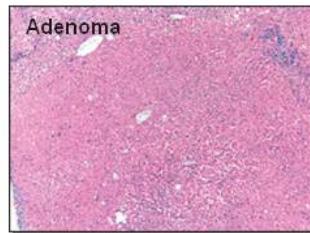
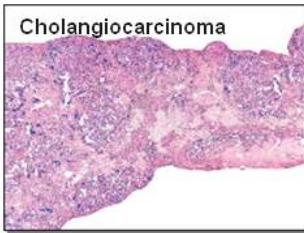
Liver

Increasing dose and time	31 weeks
– Increasing spectrum of effects	+ Oval cell hyperplasia
– Increased severity	+ Cholangiofibrosis
– Increased incidence	+ Bile duct hyperplasia
– Occurrence at lower doses	53 weeks
14 weeks	+ Foci (Eosinophilic and Mixed cell)
Hepatocyte hypertrophy	+ Cholangiocarcinoma
Fatty change, diffuse	+ Hepatocellular adenoma
Multinucleated hepatocytes	2 years
Inflammation (severity)	+ Nodular hyperplasia
Pigmentation	+ Bile duct cyst
Necrosis	+ Fatty change focal
Toxic hepatopathy	+ Hepatocholangioma + Hepatocellular carcinoma

Liver-Neoplastic lesions

	Doses ug/kg						
	0	100	220	460	1000	4600	STOP
Liver (number examined)	52	51	52	52	52	49	49
Cholangiocarcinoma	0**	0	0	0	3	36**	29**
Hepatocellular adenoma	0**	1	1	4	12**	24**	1
Hepatocholangioma	0**	0	0	0	0	4	0
Hepatocellular carcinoma	0	0	0	0	0	1	0
Cholangioma	1	0	0	0	0	0	0

** P<0.01 vs controls

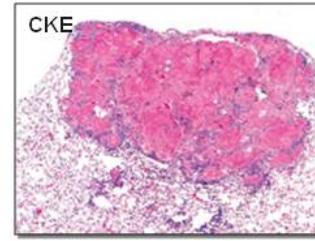
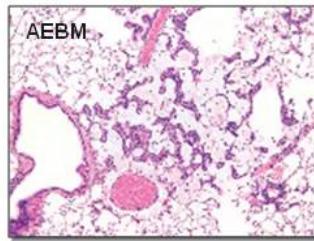
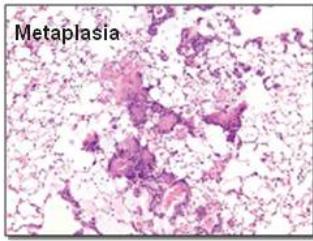




Lung

	Doses ug/kg						
	0	100	220	460	1000	4600	STOP
	51	52	52	52	52	50	50
Metaplasia, squamous	1	0	0	1	1	13**	0
Alveolar epithelium, bronchiolar, metaplasia (AEBM)	6	7	14	18**	24**	40**	32**
Cystic keratinizing epithelioma (CKE)	0**	0	0	0	0	20**	0

** P<0.01 vs controls

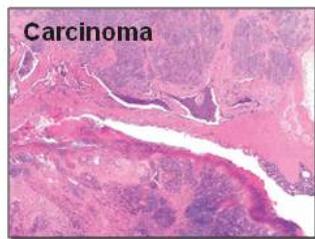




Uterus

	Doses ug/kg						STOP
	0	100	220	460	1000	4600	
Non neoplastic effects	52	52	52	52	52	52	50
Endometrium, hyperplasia, cystic	28	27	22	23	13**	9**	21
Metaplasia, squamous	29	26	27	34	35	5**	23
Neoplastic effects							
Carcinoma(A)	2	2	1	3	4	3	11*
Squamous cell carcinoma	0	0	3	1	1	0	1

** P<0.01 vs controls, *P<0.05 vs controls





Pancreas

	Doses ug/kg						
	0	100	220	460	1000	4600	STOP
Non neoplastic effects	52	52	52	52	52	47	49
Acinus, vacuolization cytoplasmic	0	0	0	0	4	42**	10
Artery, inflammation, chronic active	1	2	1	7	7	12*	5
Duct, dilatation	0	0	0	0	0	3	0
Duct, inflammation	0	0	0	0	0	2	0
Neoplastic effects							
Acinus, adenoma	0	0	0	2	3	2	0
Acinus, carcinoma	0	0	0	0	0	1	0

** P<0.01 vs controls, *P<0.05 vs controls

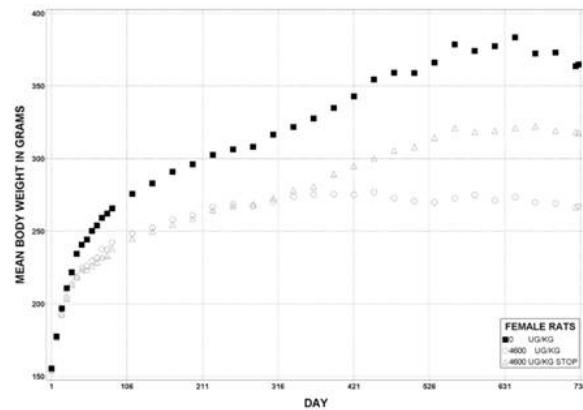


Other sites of note

	Doses ug/kg							STOP
	0	100	220	460	1000	4600		
Neoplastic effects	52	52	52	52	52	52	50	
Oral mucosa-squamous cell carcinoma	0	0	1	0	0	2	0	
Mammary gland fibroadenoma	25	29	27	33	20	8**	17	
Pituitary gland adenoma/carcinoma	19	25	18	24	17	4**	12	

** P<0.01 vs controls, *P<0.05 vs controls

- Oral mucosal neoplasms seen in other TEF studies
- Decrease in mammary and pituitary neoplasms consistent with reduced body weight gain





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Conclusions- PCB118

- Clear evidence of carcinogenic activity based on
 - Liver neoplasms
 - Cholangiocarcinoma
 - Hepatocholangioma
 - Hepatocellular adenoma
 - Lung-Cystic keratinizing epithelioma
- Were also related to treatment
 - Uterus- carcinoma
- May have been related to treatment
 - Uterus- squamous cell carcinoma
 - Pancreatic acinar neoplasms (adenoma or carcinoma)